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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,604	12/07/1999	GIOVANNI ABATANGELO	515-4181	1155

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EXAMINER

NGUYEN, QUANG

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 06/21/2002

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

09/445,604

Applicant(s)

ABATANGELO ET AL.

Examiner

Quang Nguyen, Ph.D.

Art Unit

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 June 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
- ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 03 June 2002. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet.

3. ☒ Applicant's reply has overcome the following rejection(s): Enablement 112, First Paragraph.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: None.

Claim(s) objected to: 100,102,110,111 and 119.

Claim(s) rejected: 87-99,101,103-109,112-118,120 and 121.

Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☐ Other: _____.

Continuation of 2. NOTE: New claims 132, 135-139, 142-143, 151-154 recite a specific step or a specific component that is not even present in the newly added independent claims 122 and 144. Therefore, the newly added claims 132, 135-139, 142-143 and 151-154 are ambiguous and indefinite, and this raises a new issue for Examiner to consider.

Continuation of 5. does NOT place the application in condition for allowance because: Applicants' pending claims still read over the teachings of the prior arts of record for the reasons discussed below:

1. With respect to Bellini et al. (WO 96/37519), Applicants basically argued that "ester of hyaluronic acid wherein part or all of the carboxylic groups are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic or heterocyclic series" refers to a linear polysaccharide, in which some or all of the carboxy groups are esterified with the indicated alcohol, and therefore the compounds of the presently claimed invention do not encompass the cross-linked derivative of a hyaluronic acid ester product of Bellini et al. Applicants further argued that the esters of hyaluronic acid disclosed in U.S. 4,851,521 and 5,202,431 (class A compound in the claims) do not refer in any way to crosslinked derivatives of hyaluronic acid such as those of Bellini et al., and that Bellini et al. disclosed that the esters of hyaluronic acid in US 4,851,521 are the precursors of their product. With respect to the hyaluronic acid derivatives of class B, together with the submitted Declaration under 1.132, Applicants argued that the hyaluronic acid chains are cross-linked together directly without the presence of a "spacer" molecular bridge because part of the carboxy groups of the D-glucuronic residue react directly with the hydroxy functions belonging to the same chain or to the next HA chain, forming an ester-type bond. Therefore, the polysaccharides of class B of the presently claimed invention have completely different chemical structures and physical properties from the hydrogel material of Bellini et al. Applicants' arguments are respectfully found to be unpersuasive because the claims are not limited to a matrix comprising a hyaluronic acid derivative selected from class A compound without any crosslinking or from class B compound specifically without any "spacer" molecular bridge. With respect to compound A, the claims recite a matrix comprising a hyaluronic acid derivative which is an ester of hyaluronic acid wherein part or all of the carboxylic groups of said hyaluronic acid are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic series, the matrix of Bellini et al. also comprises an ester of hyaluronic acid wherein part or all of the carboxylic groups of said hyaluronic acid are esterified with alcohols of the aliphatic or araliphatic alcohol, and therefore the matrix of Bellini et al. meets the recited limitation of the claims. Furthermore, compound C in the pending claims are clearly taught by Bellini et al.

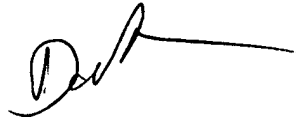
2. With respect to the combined references of Bellini et al. (WO 96/37519) and Cialdi et al. (U.S. 6,027,741), Applicants argued that Bellini et al. do not teach that their described material is a better support for the growth and proliferation of fragile cells compared to other materials usually employed as substrates for anchorage dependent cells. The hyaluronic acid derivative of Bellini et al. also differs from that disclosed of the presently claimed invention. Applicants further argued that Bellini et al. do not disclose that the hydrogel material is able to promote proliferation of the cells. Therefore, Bellini's deficiencies can not be overcome by the combined teachings with Cialdi et al. Applicants' arguments are found unpersuasive for the following reasons: First, the hyaluronic acid derivative of the instant broadly claimed invention encompasses the hyaluronic acid derivative taught by Bellini et al. for the reasons set forth in the preceeding paragraph. Compound C of the pending claims is the same as the hyaluronic acid derivative taught by Bellini et al. Second, Bellini et al. clearly teach that their hydrogel material can be used as supports of human cells including endothelial cells, Kupfer's and Langerhan's cell. There is no recitation in the pending claims that require the cells to proliferate on the matrix. Moreover, there is no factual evidence that the cells would not grow on the hydrogel material taught by Bellini et al. Please note that an embodiment of the pending claims encompasses the same teachings of Bellini et al., should Applicants doubt that the hydrogel material taught by Bellini et al. can support the proliferation of cells, then Applicants question the enablement of an embodiment of the present broadly claimed invention. With respect to the reference of Cialdi et al., Cialdi et al. clearly teach that at the effective filing date of the present application sulfated hyaluronic acid, hyaluronate esters and salts thereof can be used to prepare biomaterials in various forms such as gauzes, threads, hydrogels, sponges, membranes, non-woven tissues and microspheres. Therefore, it would also have been obvious and within the scope of skilled for an ordinary artisan to modify the hydrogel material taught by Bellini et al. in the form of a non-woven fabric, since the hydrogel material of Bellini et al. can be prepared in the form of fibers, films, membranes, threads, gauzes and sponges. With respect to Applicants' arguments that Cialdi et al. do not disclose that O-sulfated hyaluronic acid derivatives of class E can be used as substrates for the growth of cells, and that example 14 of Cialdi et al. would not induce a person of skilled in the art to use such material for the growth of endothelial cells, Examiner would like to point out that Cialdi et al. specifically teach "The new biopolymers of the present invention can also be used to advantage in cell growth processes, in controlled drug release systems" (col. 3, lines 37-49). Moreover, Cialdi et al. teach that the disclosed biopolymers can be prepared in a three dimensional forms such as threads, sponges, gauzes, membranes, non-woven fabrics et al., therefore it would have been obvious that one of ordinary skilled artisan would have been motivated to use the disclosed biopolymers in three dimensional forms to support the growth of endothelial cells. Especially, Bellini et al. already taught that numerous cell types including endothelial cells can grow on supports comprised of crosslinked hyaluronic acid esters. It should be further noted that the teachings of Cialdi et al. are not limited by example 4.

3. With respect to claims 98 and 120, although Bellini et al. do not explicitly teach isolating endothelial cells from human umbilical vein by enzymatic digestion with collagenase, amplifying the cells on collagen treated dishes in the preparation of their already disclosed hydrogel material support with endothelial cells. However, at the effective filing date of the present application, such preparation of endothelial cells from human umbilical vein for seeding on the disclosed hydrogel material of Bellini et al. is routine and well within the scope of skilled for an ordinary skilled artisan to do as evident by the state of the prior art as a whole.

4. With respect to the rejection under 112, Second paragraph, Applicants argued that the term "homologous" has a well recognized meaning in the art as the term is defined as "pertaining to genetically dissimilar individuals of the same species, allogenic" as indicated in cited reference 6. Examiner would not find the exact page number or line number where such a term is defined in reference 6 as asserted by Applicants. Since the term is also not defined by the present specification, the metes and bounds of the claims are not clearly determined. Moreover, it is noted since a cellular line is ² already defined as "a heterologous group of cells derived by the first

subculture or at any stage during the serial subculturing of a primary culture", the phrase "homologous cellular line" recited in the pending claims is certainly not clear.

Accordingly, the pending claims remain rejected for the reasons of record.



DAVE T. NGUYEN
PRIMARY EXAMINER